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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/976,596	10/12/2001	Richard Boyd	156857-0036	3119

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EXAMINER	
LI, QIAN JANICE	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 11/05/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/976,596	BOYD, RICHARD	
	Examiner	Art Unit	
	Q. Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 August 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-53* is/are pending in the application.

4a) Of the above claim(s) *22-24,29,30,33,38,47 and 50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-21,25-28,31,32,34-37,39-46,48,49 and 51-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 October 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The amendment, response, and supplemental response to the restriction requirement filed on 6/18/03 & 8/4/03 are acknowledged. Claims 1-18 have been canceled, and claims 19-53 are newly submitted.

Election/Restrictions

In view of the amendment, arguments presented in the responses, and in light of the specification, the original restriction has been modified as follows.

1. Independent inventions:

Group I, drawn to a method for inducing tolerance in a patient to a graft from a mismatched donor, comprising ablating the patient's T cells, and reactivating the patients thymus, wherein the reactivation is through surgical castration to remove the patient's gonads.

Group II, drawn to a method for inducing tolerance in a patient to a graft from a mismatched donor, comprising ablating the patient's T cells, and reactivating the patients thymus, wherein the reactivation is through administering a pharmaceutical composition to the patient to disrupt the sex steroid mediated signaling to the thymus, and a kit used in the method.

Original claim 1 or present claims 19-32, 34-40, 51, 52 are linking claims of the two groups.

2. Claims 19-32, 34-40, 51, 52 link(s) inventions II and I. The restriction requirement between the linked inventions is subject to the nonallowance of the linking claim(s), claims 19-32, 34-40, 51, and 52. Upon the allowance of the linking claim(s), the restriction requirement as to the linked inventions shall be withdrawn and any claim(s) depending from or otherwise including all the limitations of the allowable linking claim(s) will be entitled to examination in the instant application. Applicant(s) are advised that if any such claim(s) depending from or including all the limitations of the allowable linking claim(s) is/are presented in a continuation or divisional application, the claims of the continuation or divisional application may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. *In re Ziegler*, 44 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

3. Species Election:

a. Types of the cells used for transplantation,

b. Types of pharmaceutical composition used for disrupting sex steroid-mediated signaling,

c. The state of the patient

4. In the 6/18/03 response, applicants elected group II, drawn to disrupting sex steroid-mediated signaling with a LHRH agonist and transplanting hematopoietic stem cells in a patient whose thymus is at least partially deactivated.

Concordant with the election, claims 19-21, 25, 32, 34-37, 39-46, 48, 49, 51-53 are under current examination. However, claims 26-28, and 31 are rejoined to be examined together in this application as no severe search burden were imposed on the Office.

Claim Objections

Claim 35 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Specifically, the base claim (19) recites, "the donor cells are histocompatibility matched to the graft" (step c), yet dependent claim 35 recites, "the cells are collected from a mismatched donor".

Claim 44 is objected to because of the following informalities: LHRH should be spelled-out the first time it appears in the claim. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 19-21, 25-32, 34-37, 39-46, 48, 49, 51, and 52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are vague and indefinite because of the claim recitation, "a mismatched donor" in line 1, and " wherein the donor cells are histocompatibility matched to the graft in lines 7-8". The language appears to be conflicting, and the specification fails to define the term mismatch, it is uncertain, what "mismatch" encompasses, and whether applicants intend to use a histocompatibility matched or mismatched donor cells, thus the metes and bounds of the claims are unclear. Moreover, depending on the method of measurement, whether two samples are matched or mismatched may change. For example, *Scott et al* (Blood 1998;92:4864-71) teach that serologically well matched donors often have HLA class I mismatch when more sophisticated measuring method was used.

Claim 51 is vague and indefinite because of claim recitation, "enhancing compounds". It is unclear the subject of enhancement, thus the metes and bounds of claims are uncertain.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 19-21, 25-28, 31, 32, 34, 40-46, 48, 49, 51-53 are rejected under 35 U.S.C. 102(b) as being anticipated by *Ghalie et al* (Am J Hematol 1993;42:350-3).

Ghalie et al teach a method comprising ablating the patient's T cells by total body irradiation and cyclophosphamide (Patient Characteristics, page 361), reactivating the patient's thymus by administering LHRH angonist leuprolide intravenously or orally in a pharmaceutical composition before or at the time and continued after receiving donor cells (Leuprolide Administration, page 361), wherein the patient's thymus has been at least partially deactivated due to the age of the patients and by the high-dose chemotherapy and total body irradiation, wherein the patients are post-pubertal (median age 26), wherein the patients have a disease, such as leukemia or malignant lymphoma, and received autologous (histocompatibility matched to the graft) and allogenic transplantation, wherein the dosage for LHRH is 1 mg daily. *Ghalie et al* use an LHRH analog, and hematopoietic stem cells (kit) for treatment. Since the method steps meet claim limitation, the patients' peripheral T cell level would restored to that found in a pre-pubertal person. Accordingly, *Ghalie et al* anticipate instant claims.

Please note that the claim recitation "for inducing tolerance to a graft from a mismatched donor" has not been given patentable weight in this rejection and rejections that follow. This is because it merely recites an intended use of the method, wherein there is no structural or manipulative difference between the claimed invention and the prior art in order to patentably distinguishing the claimed invention from the prior art. **If the prior art structure is capable of performing the intended use, then it meets the claim.** In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 19, 34, and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Ghalie et al* (Am J Hematol 1993;42:350-3), and taken with *Nara et al* (Acta Haematol 1994;92:42-5).

Ghalie et al teach a method comprising ablating the patient's T cells by total body irradiation and cyclophosphamide (Patient Characteristics, page 361), reactivating the patient's thymus by administering LHRH angonist leuprolide intravenously or orally (Leuprolide Administration, page 361), wherein the patients received autologous (histocompatibility matched to the graft) and allogenic transplantation. *Ghalie et al* do not teach using cyclosporin as the immunosuppressant.

Nara et al teach a method comprising ablating a patient's T cells by chemotherapeutic or immunosuppressive drugs such as predinisolone, azathioprine, and cyclophosphamide (fig. 1). *Nara et al* also teach that cyclosporin is an alternative immunosuppressive agent (right column, page 42). After multiple allogenic red cell transfusion including myeloid progenitors, the patient received LHRH angonist *buserelin*

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods taught by *Ghalie et al*, by simply substituting the cyclophosphamide with the cyclosporin as taught by *Nara et al* with a reasonable expectation of success. The ordinary skilled artisan would have been

motivated to modify the claimed invention because given the choices of numerous immunosuppressants known in the art, it falls within the bounds of optimization to select one of the immunosuppressants for T cell ablation. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 19, 35-37, and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Ghalie et al* (Am J Hematol 1993;42:350-3), taken with *Hoffman et al* (US 5,744,361) and *Steinman et al* (US 5,994,126).

The teaching of *Ghalie et al* has been discussed in detail under §102, *Ghalie et al* do not discuss pre-treating the donor or donor cells with GM-CSF or expanding donor cells prior to transplantation.

Hoffman et al teach using individual or combination of cytokines such as IL-3 and GM-CSF for expanding hematopoietic stem cells ex vivo, and using such for further transplantation (abstract).

Steinman et al teach IL-3 and GM-CSF could also be given to the donor prior to collecting donor cells (column 43, § 1) to expand the myeloid progenitor cells in the blood.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods taught by *Ghalie et al* by simply including the cytokine pretreatment in the therapeutic regimen as taught by *Hoffman et al* and *Steinman et al* with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed method because the cytokine

pre-treatment would enhance the hematopoietic stem and myeloid progenitor cell contents of donor cells. As to the dosing of GM-CSF and the numbers of donor cells, given the state of the art, these limitations would fall within the bounds of optimization for stem cell transplantation. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 9:30 am - 6 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

JANICE LI
PATENT EXAMINER

Q. Janice Li
Patent Examiner
Art Unit 1632

QJL
October 29, 2003